REMARKS

This submission is in response to the Office Action mailed August 29, 2001. The Examiner has withdrawn claims 1-6, 18-28, and 30-45 from further consideration under 37 C.F.R.1.142(b), and has provisionally withdrawn claim 9 as being drawn to a non-elected species. Claims 7-17, 29, 31-41 and 43-45 have been canceled, without prejudice or disclaimer. New claims 46-65 have been added. Thus, claims 46-61 are at issue. Reconsideration of the above identified application, in view of the above amendments and the following remarks, is respectfully requested.

The subject matter of new claims 46-65 largely corresponds to that of elected claims 7-17 and 29, which have been canceled without prejudice with this amendment. The new claims are all supported by the original claims and the specification as filed, as shown in the Table below.

New claim	Original Claim	Specification
46	2-3, and 7	Figs. 1A and 1B, p. 36, l. 26 to p. 37, l. 27
47	2 and 7	Figs. 1A and 1B, p. 36, l. 26 to p. 37, l. 27
48	8 and 9	Page 36, ll. 3-24, and p. 39, ll. 9-25
49	8	Page 36, ll. 3-24
50	10	Page 36, ll. 3-24, and p. 37, l. 28 to p. 38, l. 11
51	11	Page 36, ll. 3-24, and p. 37, l. 28 to p. 38, l. 11
52	2-3, 7, and 11	Page 36, ll. 3-24, and p. 37, l. 28 to p. 38, l. 11
53	8, 9, and 11	Page 36, ll. 3-24, and p. 37, l. 28 to p. 38, l. 11
54	12	Page 36, ll. 3-24, and p. 37, l. 28 to p. 38, l. 11
55	4 and 13	Example 2, pp. 43-46

New claim	Original Claim	Specification
56	14	Example 2, p. 43, lines 24-29
57	14	Example 2, p. 43, lines 24-29
58		Example 2, p. 43, lines 24-29
59	15	Example 2, lines 6-12
60	16, 29	Example 2, lines 6-12
61	17	Example 2, lines 6-12
62	11	Page 36, ll. 3-24, and p. 37, l. 28 to p. 38, l. 11
63	2, 7, and 11	Page 36, ll. 3-24, and p. 37, l. 28 to p. 38, l. 11
64	8 and 11	Page 36, ll. 3-24, and p. 37, l. 28 to p. 38, l. 11
65	12	Page 36, ll. 3-24, and p. 37, l. 28 to p. 38, l. 11

No new matter has been added by way of this amendment.

Each of the Examiner's objections and rejections are discussed below, to the extent that the same objections and rejections may be relevant to the claims replacing the claims canceled with this response.

Priority

The Examiner contends that there is no adequate support for the nucleic acid sequence of SEQ ID NO:13 or the amino acid sequence of SEQ ID NO:14 in the priority application, U.S.S.N. 60/127,452.

Applicants disagree. The human PAMP amino acid sequences described in the priority application (SEQ ID NO:2), includes an N-terminal signal peptide

corresponding to the first 23 amino acid residues, but is otherwise the same as the human PAMP amino acid sequence of the instant application (SEQ ID NO:14).

The human PAMP nucleotide sequence in the priority application (SEQ ID NO:1) includes almost the entire coding sequence for PAMP as set forth in SEQ ID NO:13 of the instant application. One of ordinary skill in the art, in possession of the PAMP nucleotide and amino acid sequences of the priority application, could therefore easily have deduced the full sequence of SEQ ID NO:13. One of ordinary skill in the art could also have introduced mutations, using established methods, and tested them according to the methods described in the priority application at page 15, line 22 to page 16, line 5, and identified relevant mutations such as the D336, Y337, and C230 mutations and the Δ312-369 and Δ312-340 deletions. Furthermore, one of ordinary skill in the art would recognize that applicants possessed the subject matter of claims 46-61 given the written description of the prior 60/127,452 application.

Accordingly, the subject matter of the pending claims is entitled to priority from U.S.S.N. 60/127,452.

The Rejections Under 35 U.S.C. 112, 2nd Paragraph, Should Be Withdrawn

The Examiner has rejected claims 7-8, 10-17, and 29 for alleged indefiniteness. Each of the Examiner's rejection under this statue is addressed separately below.

The Examiner states that claims 7 and 10-17 depend from non-elected claims. With this amendment, claims 7 and 10-17 have been canceled, without prejudice, and new claims 46-65 do not include any claims depending from non-elected claims. Accordingly, this rejection is moot.

The Examiner contends that the terms "PAMP" and "mutant PAMP" in claims 7, 8, 13-17 and 29 are indefinite, stating that PAMP could be a functionally active epitope of not more than 5 amino acids. In contrast to the Examiner's interpretation of the phrase "PAMP", the PAMP proteins of the invention can be recognized by the very function recited in the name PAMP; Presenilin Associated Membrane Protein. "PAMP" is defined accordingly in the specification (page 8, lines 10-12):

> As referred to herein, "PAMP" means a native or mutant full-length protein, or fragment thereof, that interacts with the PAMP-interacting domain of a presenilin protein.

New claims 51, 55 and 62, specifically recite this particular feature of PAMP. The specification also describes such PAMP-presenilin "interaction" complexes, how to obtain them, and how to identify PAMP (page 34, line 23 to page 36, line 2). Moreover, detailed structural features of PAMP are described at page 8, line 21 to page 9, line 9, of the specification, and are further accentuated by the sequence alignment of four PAMP proteins from different species shown in Figure 1. In addition, new claims 46-50 recite specific PAMP sequences. In view of these

arguments, Applicants respectfully requests reconsideration and withdrawal of this rejection.

The Examiner alleges that the phrase "which is human" in claim 10 is indefinite. However, new claims 48-49 and 53 recite isolated nucleic acids, each of which comprises the coding region of a selected PAMP sequence. Accordingly, this rejection has been overcome and should be withdrawn.

The Examiner contends that the phrase "a cell..." in claims 11 and 16 is indefinite, and suggests amending the claim to "an isolated cell...". New claim 51-53, 60 and 62, all call for isolated cells. Thus, this rejection has been overcome and should be withdrawn.

The Examiner also alleges that the mutations recited in claim 14 provides no sequence context. In new claims 56-58, each mutation or deletion is related to the amino acid sequence of one of the disclosed PAMP proteins, human PAMP (SEQ ID NO:14). Thus, for new claims 56-58, the amino acid sequence for a mutant PAMP can be aligned with SEQ ID NO:14 as a reference sequence, using a suitable sequence alignment algorithm, such as, *e.g.*, that embodied in MEGALIGN, the GCG software or other sequence alignment software exemplified in the specification (see page 17, lines 20-24, and page 18, lines 11-24) to identify which residue corresponds to a position of a specific mutation set forth in the claims. Such an alignment of four PAMP proteins is shown in Figure 1. A similar analysis is also described for PS1 and PS2 mutants in the specification (page 21, lines 18-22), and could easily be applied

by one of ordinary skill in the art guided by the teachings of the disclosure. Accordingly, the new claims provides adequate sequence context for the PAMP mutations of the invention, and this rejection should be withdrawn.

The Rejections Under 35 U.S.C. 112, 1st Paragraph, Should Be Withdrawn

The Examiner alleges that claims 7, 8, 10-17, and 29 fail to meet the written description requirement. Specifically, the Examiner contends that it is not sufficient to define DNA solely by its relationship to a protein-encoding region, and that claiming all DNAs that achieve a result without defining means to do so is not in compliance with the written description requirement.

Applicants have identified, and disclose in the specification, the sequences of PAMP proteins derived from four different species (see page 8, lines 10-12, page 8, line 21 to page 9, line 9, page 34, line 23 to page 36, line 2, and Figure 1), thus providing the ***structure*** of PAMP proteins. New claims 46-50 recite specific sequences for the encoded PAMP proteins. As discussed above and as recited in new claims 51 and 55, the PAMP proteins encoded by the wild-type nucleic acids of the invention are all characterized by their capability to bind to presenilins, thus providing a ***functional feature*** of PAMP. Thus, Applicant's were clearly in possession of the invention defined by the current claims at the time of filing of the application as evidenced by the written description.

The Examiner also contends that the specification fails to provide adequate guidance for making and using PAMP nucleic acids in view of the allegedly relatively uncharacterized nature of the PAMP protein.

Applicant's respectfully disagree. The specification describes, in detail, how to identify, isolate, and characterize PAMP from four different species. For example, PAMP-presenilin complexes can be isolated by cellular extraction, followed by electrophoresis; the PAMP proteins identified, sequenced, and characterized by mass spectrometry analysis; and PAMP and PAMP mutants produced by standard molecular biology techniques (see Examples 1 and 2, pages 34-46 of the specification). A method to isolate a wild-type PAMP protein can rely on its very capability to bind to presenilin, as recited in claims 51 and 55.

The Examiner also contends that the specification does not provide sufficient guidance how to construct and use mutants since the specification fails to provide sufficient guidance concerning the particular functional domains critical to PAMP function or with an established nexus to, *e.g.*, Alzheimer's disease.

Applicants would like to draw the Examiner's attention to page 8, line 14, to page 10, line 10, of the specification. This section of the disclosure specifically describes the structural features that characterize PAMP, *e.g.*, that human PAMP is a transmembrane protein comprising various functional motifs identified via comparison with known protein/structure relationships. In addition, by comparing PAMP from different species, conserved regions such as the cyclic nucleotide binding domains and

the cysteine residues in the N-terminal hydrophilic domain can be identified, yielding further information as to the role and importance of certain PAMP motifs (page 9, line 20, to page 10, line 10).

Up-to-date, investigations of β-APP, presenilin, and their mutants, are among the few to provide reliable "biochemical" clues to the pathology of Alzheimer's disease. The compound of the present invention, PAMP, is related to these known Alzheimer's proteins in numerous ways. For example, (1) the *C. elegans* PAMP homolog plays a role in the Notch signaling pathway (page 39, lines 9-25), (2) the human PAMP gene is situated close to various Alzheimer's markers; (3) the gene for the mouse PAMP homolog is close to a known locus in which a defect creates various specific birth defects reminescent of those observed in $PS1^{-/-}$ mice (page 38, line 24 to page 39, line 39), (4) cell lines expressing pathogenic mutations of PS1 showed increased amount of C-terminal β-APP fragments co-immunoprecipitating with PAMP (page 38, lines 12-23), and (5) site-directed mutagenesis PAMP mutants of the invention showed that mutations in conserved regions of PAMP caused biochemical changes similar to those induced by mutations in the β-APP, PS1, and PS2 genes which give rise to Alzheimer's disease (page 44, lines 24-29). Taken together, these studies provide ample evidence of the involvement of PAMP in β-APP and *Notch* processing, as well as the specific features of PAMP that are implicated.

The Rejection Under 35 U.S.C. §102 Should Be Withdrawn

The Examiner has rejected claims 7, 10, 11, 13, 15, and 16 as being anticipated by GenBank Accession No. D87442 ("D87442"). Specifically, the Examiner states that D87442 differs from the human PAMP only by one (methionine) residue, and could thus be broadly interpreted as a PAMP mutant.

New claims 46-50 calls for specific PAMP sequences, which differ from that of D87442. New claims 51-54 and 60-65 calls for an isolated cell transfected with a nucleic acid encoding a PAMP protein. GenBank entry D87442 does not disclose or suggest a cell transfected with a PAMP protein. In fact, the sequence does not even disclose what the start codon of a PAMP nucleotide sequence would be, and therefore does not suggest that any corresponding protein sequence would complete.

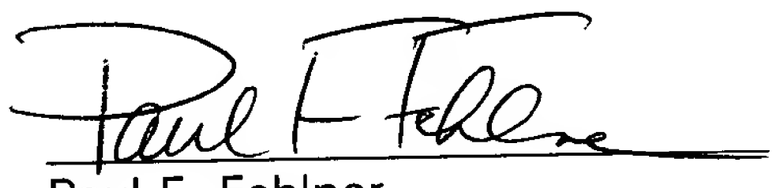
New claims 55-59 are directed to mutants of PAMP. There is no suggestion in the Gen Bank entry of mutants of this protein, or any phenotype associated with mutants. Any anticipatory reference must teach each and every aspect of the claimed invention either explicitly or impliedly (MPEP 706.02). Since the D87442 entry fails to teach or suggest cells the specific PAMP sequences recited in the claims, cells transfected with a PAMP nucleic acid, or mutant PAMP, D87442 does not anticipate the claimed invention.

CONCLUSION

Therefore, in view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,



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